Remarks/Arguments

The foregoing amendments to the claims are of a formal nature, and do not add new matter. Claims 119-138 were pending in this application and were rejected on various grounds. Claims 119-123, 127-128 and 132-134 have been canceled without prejudice or disclaimer. Claim 124 has been amended for clarity and Claim 130 has been amended for proper claim dependency. The rejections to the presently pending claims are respectfully traversed.

Sequence Rules

To comply with sequence rules, Applicants have requested the use of the sequence listing from co-pending application Serial No. 09/941992 and have enclosed the paper copy of the sequence listing. Applicants further submit that the paper copy is identical to the computer readable form of the sequence listing.

Specification

The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

In addition, amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Regarding the comment that pages 303-306 of the specification were missing, Applicants enclose a copy of the stamped return postcard received from the USPTO. This is *prima facie* evidence that all pages, including pages 303-306, were present at the time of filing of this application. For the Examiner's reference and convenience, Applicants have attached copies of pages 303-306 with this response.

Accordingly, Applicants believe that all objections to the specification has been overcome.

Claim Rejections – 35 USC § 101 and §112, first paragraph

Claims 119-138 were rejected under 35 U.S.C. §101 since allegedly "none of the asserted utilities are specific to the claimed nucleic acids, since such can be applied to any nucleic acid."

Claims 119-138 were also rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". Regarding the gene amplification data, the Examiner asserted on page 5 of the Office action that "the Examiner is unable to find either in the specification or in the art, an explanation of how Ct values are calculated, nor what the significance of such are." The Examiner concluded that "given the paucity of information, the data do not support the implicit conclusion that PRO341 shows a positive correlation with lung cancer". Further, the Examiner also alleged that since the data was not corrected for aneuploidy, and since it did not necessarily follow that an increase in gene copy number would result in increased gene expression, there was no support for the claimed nucleic acids being useful in the diagnosis of cancer. The Examiner concluded that "significant research would be required of the skilled artisan to determine whether PRO341 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic."

Without admitting to the propriety of present rejections and solely in the interest of expediting prosecution in this case, claims 119-123 and 127-128 and 132-134 have been canceled and thus, rejections to these claims should be obviated. Applicants respectfully disagree with and traverse the rejection to the remaining claims.

Applicants rely on the gene amplification assay for patentable utility in this case. This was first disclosed in U.S. Provisional Application 60/092182, filed July 9, 1998, priority to which has been claimed in this application. Hence, the effective filing date of the present application is **July 9, 1998.**

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 170 of the present application, where the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9A. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or

approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9A says that PRO341 showed approximately 1.12-1.33 ΔCt units which corresponds to $2^{1.12}$ -$2^{1.33}$- fold amplification or **2.173 fold to 2.514-fold** amplification in lung tumors. This disclosure in the specification should address the Examiner's concerns regarding calculation of Ct values.

Further, to address the Examiner's issues concerning the TaqMan™ assay, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> "It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy" (Emphasis added).

The Declaration also confirms that based upon the gene amplification results set forth in Table 9A, one of ordinary skill would find it credible that the PRO341 nucleic acid is a diagnostic marker of human lung cancer.

Regarding the Examiner's rejection based on a lack of explanation for aneuploidy, Applicants have enclosed a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, gene amplification of the PRO341 gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic for detection of lung cancer.

Applicants have demonstrated utility for the PRO341 nucleic acid and pointed out to data in the specification that clearly supports a role for the PRO341 nucleic acid as a lung tumor marker. Accordingly, the present 35 U.S.C. §101and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

1) Claims 119-138 are also rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement of the claimed variants of SEQ ID NO: 20 in the specification since there was little or no guidance beyond mere presentation of sequence. The Examiner also alleged that there was no information regarding the positions which tolerate changes or the nature/extent of changes that could be made at these positions.

In view of the cancellation of claims 119-123, 127-128 and 132-134, these rejections to these claims are obviated. Applicants respectfully disagree with and traverse the rejection of the remaining claims.

Further, Applicants submit that undue experimentation would not be required of the skilled artisan, to make and use the claimed invention as described in the specification. Hence, this rejection should be withdrawn.

2) The Examiner noted that Claims 119-124 and 131-138 encompassed nucleic acids that encoded polypeptides that were structurally defined by reference to a biological deposit, ATCC accession number 209792 and pointed out that they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public.

Applicants submit that amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Thus, this rejection is obviated.

3) Claims 119-123 and 132-138 were rejected under 35 U.S.C. 112, first paragraph since, according to Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the

claimed invention at the time of filing." The Examiner also noted that there was no description of the "extracellular domain" of the protein.

Again, in view of the cancellation of claims 119-123, 127-128 and 132-134 and the deletion of references to the "extracellular domain" in the claims, these rejections are obviated. Further, in view of the discussions presented above, Applicants submit that the skilled artisan would accept that Applicants had possession of the claimed subject matter at the time of filing.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-124, 127-128 and 132-138 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleged that the protein identified as PRO341 has several transmembrane domains while the claims recite "the extracellular domain." The Examiner alleges that if there are several transmembrane domains there must be several extracellular domains, and it is unclear which extracellular domain is intended.

In view of cancellation of claims 119-123 and 127-128 and 132-134, rejections to these claims are obviated. Further, parts (c) and (d) of the claim have been deleted for clarity. Accordingly, Applicants submit that the claims are definite and respectfully request that this rejection be withdrawn.

Claim Rejections - 35 USC § 102

Claims 132-134 are rejected under 35 U.S.C. §102(e) as being anticipated by Conklin et al. (U.S.P.N. 6046028, effective filing date 10/15/96.

In view of cancellation of claims 132-134, this rejection is obviated and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C48).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 7, 2004

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